UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/009,581	04/30/2002	Mortimer M. Civan	L-2070	1751

67283 7590 03/29/2010

MONTGOMERY, MCCRACKEN, WALKER & RHOADS, LLP
123 SOUTH BROAD STREET
AVENUE OF THE ARTS
PHILADELPHIA, PA 19109

EXAMINER	
JAGOE, DONNA A	

ART UNIT	PAPER NUMBER
1619	

MAIL DATE	DELIVERY MODE
03/29/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/009,581	CIVAN ET AL.	
	Examiner	Art Unit	
	Donna Jagoe	1619	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 August 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *94-104,107-110,112,113,115 and 116* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *94-104,107-110,112,113,115 and 116* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 94-104, 107-110, 112, 113, 115 and 116 are pending in this application.

Applicants' arguments filed August 18, 2009 have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 112 (first paragraph)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 101 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In particular, "a latanoprost precursor prostaglandins" is a concept that was not present in the specification as originally filed. Applicants are advised that the issue here

is not whether particular instance of a prostaglandin precursor, but rather whether the concept of other prostaglandin precursors other than latanoprost" was present in the specification as originally filed.

The specification as originally filed contains the following disclosures concerning a prostaglandin inhibitor:

(i) "another new type of drug, precursor prostaglandin compounds (e.g., latanoprost) are also in current use". (page 3, lines 27-28).

The above disclosure, however, does not provide adequate support for "a latanoprost precursor prostaglandins". Prostaglandin precursors include essential fatty acids, such as arachidonic acid, linoleic acid, eicosapentanoic acid and dihomogammalinoleic acid. There does not seem to adequate support in the specification for any of these prostaglandin precursors.

An Applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams and formula that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997).

The Examiner is guided in his opinion that Applicant has not adequately described the presently claimed subject matter by the MPEP at § 2163 - 2163.05. In particular, while Applicant's specification as originally filed contained a specific reference to latanoprost as being one example of a prostaglandin precursor but such does not entitle Applicants to now claim all prostaglandin precursors because such represents a subgenus that was not previously set forth or one that would have been

immediately envisaged by one skilled in the art from the specification as originally filed. "A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process. See, e.g., Fujikawa v. Wattanasin, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996)"(emphasis added), see MPEP § 2163(I)(A). Also, "See also In re Smith. 458 F.2d 1389, 1395, 173 USPQ 679, 683 (CCPA 1972) ('Whatever may be the viability of an inductive-deductive approach to arriving at a claimed subgenus, it cannot be said that such a subgenus is necessarily described by a genus encompassing it and a species upon which it reads.' (emphasis added))."., see MPEP § 2163.05(II). A "latanoprost precursor prostaglandins" includes agents such as misoprostol, used in treatment of duodenal and gastric ulcers. Because latanoprost is the only contemplated prostaglandin precursor, a person of ordinary skill in the art would not view the applicant to have been in possession of the generic subject matter claimed based on the single species disclosed in the specification. There is no disclosure or guidance regarding what structures are necessary and what structure to function correlations are necessary to define and identify any other members of the claimed subgenus.

Considering the teachings provided in the specification as originally filed, the Examiner finds that Applicants have failed to provide the necessary teachings, by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams and formula that fully set for the claimed

invention, in such a way as to reasonably convey to one skilled in the relevant art that Applicants had possession of the concept of a “a latanoprost precursor prostaglandins”.

Claims 94-104, 107-110, 112, 113, 115 and 116 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In particular, “wherein the method for therapeutically reducing aqueous humor inflow by selectively inhibiting sodium-hydrogen antiport activity in the eye of a human or animal subject” and wherein "the NHE inhibitor selectively inhibits cellular antiport activity" (present claims 94 and 108) is a concept that was not present in the specification as originally filed. Applicants are advised that the issue here is not whether particular instances of NHE inhibitors are effective at low concentrations are disclosed, but rather whether the concept of “the NHE inhibitor functions as **selective** inhibitor at very low concentrations” was present in the specification as originally filed. The Examiner contends that such a concept, of selective inhibition with regard to inhibition at one component without inhibition at any other component, was not present in the specification as originally filed.

The specification as originally filed contains the following disclosures concerning NHE concentration:

(i) This discovery is particularly relevant because of the known sensitivity of **the exchanger** to a number of drugs; which are effective at **very low concentrations**. Consequently, in accordance with the present invention, control of the exchanger permits control or regulation of the secretion of the aqueous humor, permitting the prevention or modulation of the fluid in the intraocular space." (page 5, lines 20-24);

(ii) "...a Na+/proton exchanger as the antiport, permits strategies to be developed to use drugs at very low, focussed (sic) concentrations for preventing, modulating or regulating intraocular pressure, most particularly for treating or reducing elevated intraocular pressure." (page 11, lines 23-26);

The above disclosures, however, do not provide adequate support for the concept of whether the "NHE inhibitor functions as **selective** inhibitor at very low concentrations" and "selectively inhibiting cellular antiport activity". The instant specification does not describe how one would practice *selective* inhibition. Further, what route of administration or dosage would accomplish *selective* inhibition of the antiport without inhibiting other antiports/symports.

Written Description

An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams and formula that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997).

The Examiner is guided in his opinion that Applicant has not adequately described the presently claimed subject matter by the MPEP at § 2163 - 2163.05. In

particular, while Applicant points to page 5 lines 20-21 and lines 29-30 for support in the specification, the recitation of "this discovery is particularly relevant because of the known sensitivity of the exchanger to a number of drugs which are effective at very low concentrations" (page 5, lines 20-21) and "low dosages permit the drugs to be used without any or with minimal adverse side-effects does not specifically link the NHE inhibitor to administration of very low dosages in this citation because such represents a concept that were not previously set forth or that would have been immediately envisaged by one skilled in the art from the specification as originally filed. "A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process. See, e.g., *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996)"(emphasis added), see MPEP § 2163(I)(A). Also, "See also *In re Smith*. 458 F.2d 1389, 1395, 173 USPQ 679, 683 (CCPA 1972) ('Whatever may be the viability of an inductive-deductive approach to arriving at a claimed subgenus, it cannot be said that such a subgenus is necessarily described by a genus encompassing it and a species upon which it reads.' (emphasis added)).", see MPEP § 2163.05(II).

Considering the teachings provided in the specification as originally filed, the Examiner finds that Applicants have failed to provide the necessary teachings, by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams and formula that fully set for the claimed invention, in such a way as to reasonably convey to one skilled in the relevant art that

Applicants had possession of the concept of an NHE inhibitor that functions as a selective inhibitor at very low concentrations.

Claim Rejections - 35 USC § 112 (second paragraph)

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 113 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 113 recites the limitation "The method of claim 112, wherein the amiloride analog is" in line 1 of the claim. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 94-96, 102 and 107 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Cherksey U.S. Patent No. 4,950,591.

The claims are drawn to the method for reducing aqueous humor inflow by selectively inhibiting sodium-hydrogen antiport activity in the eye of a human or animal subject comprising administering a pressure modulating amount of at least one sodium-hydrogen exchange inhibitor (NHE inhibitor) to selectively inhibit cellular antiport activity wherein the NHE inhibitor displaying an inhibitor constant (Ki) characteristic of NHE-1 antiport blockers; thereby inhibiting the activity of the sodium hydrogen antiport(s) and as a result, reducing net inflow in aqueous humor formation. Instant claim 96 identifies the NHE inhibitor as an amiloride.

Cherksey teaches amiloride is an agent that **selectively** blocks ion transport and interacts with a Sodium Hydrogen Exchange (NHE) inhibitor at high concentrations and with the Na+ channel protein at much lower concentrations (column 1, lines 21-27) . Amiloride and derivatives are capable of regulating membrane transport, **cellular volume** or **cellular pressure disorders** (column 2, lines 5-10). The amiloride derivatives are **useful when applied topically for the treatment of glaucoma** (column 3, line 66 to column 4, line 3 and column 5, lines 42-47). Regarding the limitations of instant claim 94, drawn to the concept of the NHE inhibitor displaying an inhibitor constant (Ki) characteristic of NHE-1 antiport blockers, as noted in *In re Best* (195 USPQ 430 (CCPA 1977)), and *In re Fitzgerald* (205 USPQ 594 (CCPA 1980)), the mere recitation of newly-discovered function or property, inherently possessed by things in prior art, does not cause claims drawn to those things to distinguish over prior art. In

such a situation, the burden is shifted to the applicant to prove that subject matter shown to be in prior art does not possess characteristic relied on where it has reason to believe that functional limitation asserted to be critical for establishing novelty in claimed subject matter may be inherent characteristic of prior art; whether rejection is based on "inherency" under 35 U.S.C. 102, on "prima facie obviousness" under 35 U.S.C. 103, jointly or alternatively, burden of proof is same.

Claims 94 and 101-104 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Drug Facts and Comparisons (1994).

The claims are drawn to the method for reducing aqueous humor inflow by selectively inhibiting sodium-hydrogen antiport activity in the eye of a human or animal subject comprising administering a pressure modulating amount of at least one sodium-hydrogen exchange inhibitor (NHE inhibitor) to selectively inhibit cellular antiport activity wherein the NHE inhibitor displaying an inhibitor constant (Ki) characteristic of NHE-1 antiport blockers; thereby inhibiting the activity of the sodium hydrogen antiport(s) and as a result, reducing net inflow in aqueous humor formation. Page 6 of Applicant's instant specification identifies **NHE inhibitors and inclusive of β-blockers** (see page 6, lines 23-29, see also page 13, lines 11-26).

Drug Facts and Comparisons teach timolol, a beta-blocker, to be employed topically to the eye to a human to reduce **elevated** and normal intraocular pressure with or without glaucoma (page 2287). The mechanism appears to be a **reduction of aqueous production**, and a slight **increase in outflow facility**. Regarding claims to regulating salt uptake or release by ciliary epithelial cells of the human eye by

modulation of the antiports, this action is considered to be inherent. Applicants' attention is directed to *Ex parte Novitski*, 26 USPQ2d 1389 (BOPA 1993) illustrating anticipation resulting from inherent use, absent a *haec verba* recitation for such utility. In the instant application, as in Ex *parte Novitski*, supra, the claims are directed to preventing a malady or disease with old and well-known compounds or compositions. It is now well-settled law that administering compounds inherently possessing a protective utility anticipates claims directed to such protective use. Arguments that such protective use is not set forth *haec verba* are not probative. Prior use for the same utility clearly anticipates such utility, absent limitations distancing the proffered claims from the inherent anticipated use. Attempts to distance claims from anticipated utilities with specification limitations will not be successful. At page 1391, *Ex parte Novitski*, supra, the Board said "We are mindful that, during the patent examination, pending claims must be interpreted as broadly as their terms reasonably allow. *In re Zletz*, 893 F.2d 319, 13 USPQ2d 1320 (Fed. Cir. 1989). In the instant application, Applicants' failure to distance the proffered claims from the anticipated utility renders such claims anticipated by the prior inherent use. Regarding administration of the composition to the ciliary epithelial cells of the eye, there does not seem to be any description of how one would bypass administering an eyedrop to an eye to administer said compositions to the ciliary epithelial cells of the eye. A prior art reference may anticipate without disclosing a feature of the claimed invention, if that missing characteristic is necessarily present, or inherent, in the single anticipating reference. Continental Can Co. v. Monsanto Co., 948 F.2d 1264, 1268 (Fed. Cir. 1991). Other precedents of the court have held that

inherent anticipation does not require that a person of ordinary skill in the art at the time would have recognized the inherent disclosure. E.g., *In re Cruciferous Sprout Litig.,* 301 F.3d 1343, 1351 (Fed. Cir. 2002); *Mehl/Biophile Int'l Corp. v. Milgraum*, 192 F.3d 1362, 1366 (Fed. Cir. 1999) ("Where the result is a *necessary consequence* of what was deliberately intended, it is of no import that the article's authors did not appreciate the results."); Atlas Powder, 190 F.3d at 1348-49 ("Because 'sufficient aeration' was inherent in the prior art, it is irrelevant that the prior art did not recognize the key aspect of [the] invention. An inherent structure, composition, or function is not necessarily known."). In the instant case, the unappreciated anticipation also does not require recognition. Applicant claims to have discovered the method of reducing aqueous humor inflow by modulating the antiports of the aqueous humor. Since the pharmaceutical compositions claimed by Applicant produced the claimed modulation of aqueous secretion, the discovery of the modulation of the antiport is inherent. In the context of the accidental anticipation, beta-blockers, such as timolol, do not accidentally modulate the antiport when the pharmaceutical composition is applied to a patient in need of treatment. The antiport necessarily and inevitably is modulated when the beta-blocker is applied and does not require a skilled artisan to recognize the inherent characteristic in the prior art that anticipates the claimed invention. Regarding the limitations of instant claim 94, drawn to the concept of the NHE inhibitor displaying an inhibitor constant (Ki) characteristic of NHE-1 antiport blockers, as noted in *In re Best* (195 USPQ 430 (CCPA 1977)), and *In re Fitzgerald* (205 USPQ 594 (CCPA 1980)), the mere recitation of newly-discovered function or property, inherently possessed by things

in prior art, does not cause claims drawn to those things to distinguish over prior art. In such a situation, the burden is shifted to the applicant to prove that subject matter shown to be in prior art does not possess characteristic relied on where it has reason to believe that functional limitation asserted to be critical for establishing novelty in claimed subject matter may be inherent characteristic of prior art; whether rejection is based on "inherency" under 35 U.S.C. 102, on "prima facie obviousness" under 35 U.S.C. 103, jointly or alternatively, burden of proof is same.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 94-96, 99-104, 107-110, 112, and 113 are rejected under 35 U.S.C. 103(a) as being unpatentable over Adorante et al. U.S. Patent No. 5,559,151 and Cherksey U.S. Patent No. 4,950,591.

The claims are drawn to the method for reducing aqueous humor inflow by selectively inhibiting sodium-hydrogen antiport activity in the eye of a human or animal subject comprising administering a pressure modulating amount of at least one sodium-hydrogen exchange inhibitor (NHE inhibitor) to selectively inhibit cellular antiport activity wherein the NHE inhibitor displaying an inhibitor constant (Ki) characteristic of NHE-1 antiport blockers; thereby inhibiting the activity of the sodium hydrogen antiport(s) and as a result, reducing net inflow in aqueous humor formation, and further comprising an anion exchanger isoform 2 (AE2) such as 4,4'-diisothiocyanatostilbene-2,2'-disulfonate (DIDS).

Adorante et al. teach pharmaceutical compositions and methods for treating glaucoma and/or ocular hypertension comprising administering to the mammalian eye an agent such as 4,4'-diisothiocyantostilbene-2,2'-disulfonate (DIDS) (see column 5, lines 10-18). It is noted that Adorante et al. identifies this agent as a chloride channel blocker. The identification of the agent DIDS as a chloride channel blocker does not

detract from the teaching that this agent, when it is administered to the mammalian eye, treats ocular hypertension/glaucoma because the chloride-dependent ion flux pathways will inhibit aqueous humor formation and thus, lower intraocular pressure (IOP) (column 5, lines 45-49). Adorante further teaches that drugs currently utilized in the treatment of glaucoma include, *inter alia*, miotics, sympathomimetics, beta blockers, alpha-2-agonists and carbonic anhydrase inhibitors. Miotics and sympathomimetics are believe to lower intraocular pressure by increasing the outflow of aqueous humor while β-blockers, α-2 agonists and carbonic anhydrase inhibitors are believe to lower intraocular pressure by decreasing the formation of aqueous humor. In vitro (see example, column 5) and in vivo (see claim 1) use are clearly disclosed.

Adorante et al. fails to teach co administration of NHE/NHE-1 inhibitors.

Cherksey teaches amiloride (an amiloride derivative by the definition in the instant specification at page 6, line 27) (NHE inhibitor/NHE-1 inhibitor) is an agent that selectively blocks ion transport and interacts with a Sodium Hydrogen Exchange inhibitor at high concentrations (column 1, lines 21-27). Amiloride and derivatives are capable of regulating membrane transport, cellular volume or cellular pressure disorders (column 2, lines 5-10). The amiloride derivatives are useful when applied topically for the treatment of glaucoma (column 3, line 66 to column 4, line 3 and column 5, lines 42-47).

As stated in *In re Kerkhoven*, 626 F.2d 846, 205 USPQ 1069, at page 1072 (CCPA 1980):

It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition which is

to be used for the very same purpose. In re Susi, 58 CCPA 1074, 1079-80, 440 F.2d 442, 445, 169 USPQ 423, 426 (1971); In re Crockett, 47 CCPA 1018, 1020-21, 279 F.2d 274, 276-77, 126 USPQ 186, 188 (CCPA 1960). As this court explained in Crockett, the idea of combining them flows logically from their having been individually taught in the prior art.

It would have been made obvious to one of ordinary skill in art at the time it was made to employ two agents well-known to treat glaucoma/ocular hypertension together to treat the very same condition. Adorante et al. teach that DIDS treats glaucoma and/or ocular hypertension by inhibiting aqueous humor formation and thus, lowering IOP. Cherksey teaches amiloride (NHE inhibitor/NHE-1 inhibitor) is an agent that selectively blocks ion transport and interacts with a Sodium Hydrogen Exchange inhibitor at high concentrations (column 1, lines 21-27). Amiloride and derivatives are capable of regulating membrane transport, cellular volume or cellular pressure disorders. One would have been motivated to combine these treatments motivated by the reasoned expectation of producing a composition, which is effective in comprehensively treating persons suffering from elevated intraocular pressure and glaucoma.

Regarding claims drawn to regulating salt uptake or release by ciliary epithelial cells of the human eye or eye of an animal having a trabecular meshwork (network) by controlling or modulating the function of one or more antiports of the aqueous humor ciliary epithelial cells by administering to the ciliary epithelial cells of the aqueous humor a modulating amount of a pharmaceutical composition consisting essentially of an NHE inhibitor, and the NHE inhibitor that functions as a selective inhibitor at very low concentrations, displaying an inhibitor constant (Ki) characteristic of NHE-1 antiport

blockers, as noted in *In re Best* (195 USPQ 430 (CCPA 1977)), and *In re Fitzgerald* (205 USPQ 594 (CCPA 1980)), the mere recitation of newly-discovered function or property, inherently possessed by things in prior art, does not cause claims drawn to those things to distinguish over prior art. In such a situation, the burden is shifted to the applicant to prove that subject matter shown to be in prior art does not possess characteristic relied on where it has reason to believe that functional limitation asserted to be critical for establishing novelty in claimed subject matter may be inherent characteristic of prior art; whether rejection is based on "inherency" under 35 U.S.C. 102, on "prima facie obviousness" under 35 U.S.C. 103, jointly or alternatively, burden of proof is same.

Claims 94-98, 102-104, 107-110, 112, 113 and 115 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brandt et al. U.S. Patent No. 5,585,401 and Cherksey U.S. Patent No. 4,950,591.

The claims are drawn to the method for reducing aqueous humor inflow by selectively inhibiting sodium-hydrogen antiport activity in the eye of a human or animal subject comprising administering a pressure modulating amount of at least one sodium-hydrogen exchange inhibitor (NHE inhibitor) to selectively inhibit cellular antiport activity wherein the NHE inhibitor displaying an inhibitor constant (Ki) characteristic of NHE-1 antiport blockers; thereby inhibiting the activity of the sodium hydrogen antiport(s) and as a result, reducing net inflow in aqueous humor formation, and further comprising a

pharmaceutical composition comprising an inhibitor of a Na^+-K^+-$2Cl^-$ symport such as bumetanide (claim 98).

Brandt et al. teach the administration of compounds that inhibit the function of Na^+-K^+-$2Cl^{-2}$ cotransporter mechanism (symport) in trabecular meshwork cells (see abstract) such as bumetanide for topical administration (column 6, lines 30-43). It has been discovered that the trabecular meshwork of the mammalian eye regulate cell volume and fluid transport by means of the Na^+-K^+-$2Cl^{-2}$ cotransporter mechanism. Compounds that substantially inhibit operation of this mechanism also increase the outflow of the ocular fluids, thus lowering intraocular pressure for treatment of ocular hypertension and glaucoma (column 6, lines 15-29). Brandt teaches that the cotransporter mediates a net uptake of sodium potassium and chloride into the cell (regulating salt uptake) (column 4, line 66 to column 5, line 2) Figures 1A and 1B show bovine trabecular meshwork (TM) cells (also known as trabecular network) exhibiting a total K uptake wherein bumetanide decreased the K influx (modulated salt uptake and selectively modulated the function of one of the antiports) (column 19, lines 42-51). Brandt et al. fails to teach coadministration of NHE/NHE-1 inhibitors.

Cherksey teaches amiloride (NHE inhibitor/NHE-1 inhibitor) is an agent that selectively blocks ion transport and interacts with a Sodium Hydrogen Exchange inhibitor at high concentrations (column 1, lines 21-27). Amiloride and derivatives are capable of regulating membrane transport, cellular volume or cellular pressure disorders (column 2, lines 5-10). The amiloride derivatives are useful when applied topically for

the treatment of glaucoma (column 3, line 66 to column 4, line 3 and column 5, lines 42-47).

As stated in In re Kerkhoven, 626 F.2d 846, 205 USPQ 1069, at page 1072 (CCPA 1980):

> It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition which is to be used for the very same purpose. In re Susi, 58 CCPA 1074, 1079-80, 440 F.2d 442, 445, 169 USPQ 423, 426 (1971); In re Crockett, 47 CCPA 1018, 1020-21, 279 F.2d 274, 276-77, 126 USPQ 186, 188 (CCPA 1960). As this court explained in Crockett, the idea of combining them flows logically from their having been individually taught in the prior art.

It would have been made obvious to one of ordinary skill in art at the time it was made to employ two agents well-known to treat glaucoma/ocular hypertension together to treat the very same condition. Adorante et al. teach that DIDS treats glaucoma and/or ocular hypertension by inhibiting aqueous humor formation and thus, lowering IOP. Cherksey teaches amiloride (NHE inhibitor/NHE-1 inhibitor) is an agent that selectively blocks ion transport and interacts with a Sodium Hydrogen Exchange inhibitor at high concentrations (column 1, lines 21-27). Amiloride and derivatives are capable of regulating membrane transport, cellular volume or cellular pressure disorders. One would have been motivated to combine these treatments motivated by the reasoned expectation of producing a composition which is effective in comprehensively treating persons suffering from elevated intraocular pressure and glaucoma. Regarding administration of the composition to the ciliary epithelial cells of the aqueous humor, there does not seem to be any description of how one would bypass administering an eyedrop to an eye to administer said compositions to the ciliary epithelial cells of the

aqueous humor. A prior art reference may anticipate without disclosing a feature of the claimed invention, if that missing characteristic is necessarily present, in the single anticipating reference. Continental Can Co. v. Monsanto Co., 948 F.2d 1264, 1268 (Fed. Cir. 1991).

Regarding claims drawn to regulating salt uptake or release by ciliary epithelial cells in the eye of a human or animal subject in need of such wherein the subject has a trabecular network comprising selectively controlling or modulating the function of one or more antiports of the ciliary epithelial cells of the aqueous humor by administering to the cells a modulating amount of a pharmaceutical composition which is an antiport-selective inhibitor consisting essentially of an NHE inhibitor wherein the NHE inhibitor functions as a selective inhibitor at very low concentrations, displaying an inhibitor constant (Ki) characteristic of NHE-antiport blockers; thereby regulating salt uptake or release in aqueous humor formation and reducing net inflow, Brandt teaches that the cotransporter mediates a net uptake of sodium potassium and chloride into the cell (regulating salt uptake) (column 4, line 66 to column 5, line 2) Figures 1A and 1B show bovine trabecular meshwork (TM) cells (also known as trabecular network) exhibiting a total K uptake wherein bumetanide decreased the K influx (modulated salt uptake and selectively modulated the function of one of the antiports) (column 19, lines 42-51). And teaches that drugs currently used to treat glaucoma can be divided into those that reduce aqueous humor inflow and those that enhance aqueous humor outflow that the most commonly prescribed drugs are β adrenergic antagonists (β blockers) (column 5, lines 47-55)(such as those currently claimed as NHE inhibitors). Further, as noted in *In*

re Best (195 USPQ 430 (CCPA 1977)), and *In re Fitzgerald* (205 USPQ 594 (CCPA 1980)), the mere recitation of newly-discovered function or property, inherently possessed by things in prior art, does not cause claims drawn to those things to distinguish over prior art. In such a situation, the burden is shifted to the applicant to prove that subject matter shown to be in prior art does not possess characteristic relied on where it has reason to believe that functional limitation asserted to be critical for establishing novelty in claimed subject matter may be inherent characteristic of prior art; whether rejection is based on "inherency" under 35 U.S.C. 102, on "prima facie obviousness" under 35 U.S.C. 103, jointly or alternatively, burden of proof is the same. Regarding the limitation of instant claims 94 and 108, drawn to the NHE inhibitor that functions as a selective inhibitor at very low concentrations, displaying an inhibitor constant (Ki) characteristic of NHE-1 antiport blockers, and claim 115 wherein “an anion is transferred into the ciliary epithelial cells of the aqueous humor to block native chloride channels, as noted in *In re Best* (195 USPQ 430 (CCPA 1977)), and *In re Fitzgerald* (205 USPQ 594 (CCPA 1980)), the mere recitation of newly-discovered function or property, inherently possessed by things in prior art, does not cause claims drawn to those things to distinguish over prior art. In such a situation, the burden is shifted to the applicant to prove that subject matter shown to be in prior art does not possess characteristic relied on where it has reason to believe that functional limitation asserted to be critical for establishing novelty in claimed subject matter may be inherent characteristic of prior art; whether rejection is based on "inherency" under 35 U.S.C.

102, on "prima facie obviousness" under 35 U.S.C. 103, jointly or alternatively, burden of proof is same.

Claim 116 is rejected under 35 U.S.C. 103(a) as being unpatentable over Brandt et al. U.S. Patent No. 5,585,401 and Cherksey U.S. Patent No. 4,950,591 as applied to claims 94-98, 102-104, 107-110, 112, 113 and 115 above, and further in view of Adorante et al. et al. (U).

Adorante et al. teach relative changes in E_m of non-pigmented epithelial cells (NPE) during hypoosmotic cell swelling under isoosmotic conditions and hypoosmotic conditions. The anion sodium cyclamate replaced NaCl in NPE cells under isoosmotic conditions, reducing Cl^- by about 39%, indicating that Cl^- conductance is low in IR medium (see fig. 4, page C725). Although Adorante does not teach a blocked chloride channel, it teaches a reduction of Chloride by 39% indicating a blockage.

Thus the claims fail to patentably distinguish over the state of the art as represented by the cited references. Accordingly, for the above reasons, the claims are deemed properly rejected and none are allowed.

Response to Arguments

Regarding the lack of written description of claim 101, Applicant states that "because Latanoprost exemplifies at least one compound from the group of precursor prostaglandins" it satisfies the requirement of the law and the specification where it refers to “latanoprost" as "another new type of drug...also in current use" and one of ordinary skill in the art would therefore be familiar with such drugs if they are in current

use. Applicant further states that claim 101 has been amended to recite "a latanoprost type precursor prostaglandin"; however, the claim recites "**a latanoprost precursor prostaglandins**". The amendment to the claim does not overcome the rejection under 35 U.S.C. § 112 1st paragraph. Because latanoprost is the only contemplated prostaglandin precursor, a person of ordinary skill in the art would not view the Applicant to have been in possession of the generic subject matter claimed based on the single species disclosed in the specification.Please see the rejection made supra.

Regarding the word analog in instant claims 96, 112 and 113, the rejection under 35 USC § 112, second paragraph has been withdrawn, however, please see new rejection under 35 USC § 112, second paragraph for lack of antecedent basis of instant claim 113 supra.

Claims 94-96, 102 and 107 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Cherksey U.S. Patent No. 4,950,591.

Applicant incorrectly states that claims 94-96, 102 and 105-107 are rejected under 102(b) as being anticipated by Cherksey. Claims 105 and 106 have been cancelled. In response to the rejection, Applicant states that Cherksey does not teach any interaction with a sodium-hydrogen exchange inhibitor. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., amiloride is not utilized by Cherksey at pH 4.5 suitable for actual administration to the eye) are not recited in the rejected claim(s). With regard to the administration step, there is no active step claimed,

different from the prior art cited that would result in *selective* inhibition of one antiport/channel versus another. Therefore, since Cherksey et al meets the only active limitation of administration of the same compounds, and since the art teaches that administration of amiloride inhibits the antiport, the method of the art meets the instant claim requirements. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Applicants' reliance on the post filing date references is not persuasive. The determination of obviousness or nonobviousness must be based upon what was known in the art at the time the invention was made. See 35 U.S.C. § 103: "A patent may not be obtained…if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious **at the time the invention was made** to a person having ordinary skill in the art".

Applicant states that there are multiple interacting causes of increased intraocular pressure and it would be impermissible to use inhibitors that are neither taught nor suggested in Applicants' invention, nor claimed. It is unclear what part of the rejection that Applicant feels is not part of the invention. Instant claim 96 clearly states that "an amiloride" is a NHE inhibitor. Cherksey teaches amiloride is an agent that selectively blocks ion transport and interacts with a Sodium Hydrogen Exchange (NHE) inhibitor at high concentrations and with the Na+ channel protein at much lower concentrations (column 1, lines 21-27) . Amiloride and derivatives are capable of regulating membrane transport, **cellular volume** or **cellular pressure disorders**

(column 2, lines 5-10). The amiloride derivatives are **useful when applied topically for the treatment of glaucoma** (column 3, line 66 to column 4, line 3 and column 5, lines 42-47). Applicant states that "There is no evidence that the cited prior art affects or inhibits the sodium-hydrogen antiports, or that, in fact, Cherksey's method operates on the sodium-hydrogen antiports at all since there are many components to the control of intraocular pressure". In response, there is no active step claimed, different from the prior art cited that would result in *selective* inhibition of one antiport/channel versus another. Therefore, since Cherksey et al meets the only active limitation of administration of the same compounds, and since the art teaches that administration of amiloride inhibits the antiport, the method of the art meets the instant claim requirements.

Further, Applicants' reliance on the post filing date reference, Avila et al., to allegedly provide evidence is not persuasive. The determination of obviousness or nonobviousness must be based upon what was known in the art at the time the invention was made. See 35 U.S.C. § 103: "A patent may not be obtained…if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious **at the time the invention was made** to a person having ordinary skill in the art". Further, the claims are drawn to the method for reducing aqueous humor inflow by selectively inhibiting sodium-hydrogen antiport activity in the eye of a human or animal subject comprising administering a pressure modulating amount of at least one sodium-hydrogen exchange inhibitor (NHE inhibitor) to selectively inhibit cellular antiport activity wherein the NHE

inhibitor displaying an inhibitor constant (Ki) characteristic of NHE-1 antiport blockers; thereby inhibiting the activity of the sodium hydrogen antiport(s) and as a result, reducing net inflow in aqueous humor formation. Instant claim 96 identifies the NHE inhibitor as an amiloride. This is the very same active agent. Products of identical chemical composition (i.e. an amiloride) can not have mutually exclusive properties." A chemical compound and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims (i.e. inhibition of the sodium-hydrogen antiports) are necessarily present. In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Applicant states that "Cherksey claims the use of amiloride solely for the use of the isolated peptide as a diagnostic and experimental tool, whereas by comparison, Applicants' invention neither teaches, nor claims, a method for regulating the "sodium channel" or its role in aqueous humor formation." In response, The Examiner directs Applicant's attention to *In re Heck*, 699 F.2d 1331, 1332-33, 216 USPQ 1038, 1039 (Fed. Cir. 1983) (quoting *In re Lemelson*, 397 F.2d 1006, 1009, 158 USPQ 275, 277 (CCPA 1968)). "The use of patents as references is not limited to what the patentees describe as their own inventions or to the problems with which they are concerned. They are part of the literature of the art, relevant for **all** they contain." A reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. Further, *Merck & Co. v. Biocraft Laboratories*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), *cert. denied,* 493 U.S. 975 (1989). See also *Upsher-Smith Labs. v. Pamlab,LLC*, 412 F.3d 1319, 1323, 75 USPQ2d 1213, 1215 (Fed. Cir.

2005) (reference disclosing optional inclusion of a particular component teaches compositions that both do and do not contain that component). Cherksey teaches amiloride is an agent that **selectively** blocks ion transport and **interacts with a Sodium Hydrogen Exchange (NHE) inhibitor** at high concentrations and with the Na+ channel protein at much lower concentrations (column 1, lines 21-27) . Amiloride and derivatives are capable of regulating membrane transport, **cellular volume** or **cellular pressure disorders** (column 2, lines 5-10). The amiloride derivatives are **useful when applied topically for the treatment of glaucoma** (column 3, line 66 to column 4, line 3 and column 5, lines 42-47). Consequently, this argument does not raise an issue of material fact.

Claims 94 and 102-104 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Drug Facts and Comparisons (1994).

Applicant asserts that timolol was not recognized by those knowledgeable in the field to be a NHE inhibitor. In response, where an **explicit definition** is provided by the Applicant for a term, that definition will control interpretation of the term as it is used in the claim. *Toro Co. v. White Consolidated Industries Inc.*, 199 F.3d 1295, 1301, 53 USPQ2d 1065, 1069 (Fed. Cir. 1999) (meaning of words used in a claim is not construed in a "lexicographic vacuum, but in the context of the specification and drawings."). Applicant argues that the reference offers no evidence that timolol achieved any inhibition of sodium-hydrogen antiport activity in the ciliary epithelial cells. In response, a prior art reference may anticipate without disclosing a feature of the claimed invention if that missing characteristic is necessarily present, or inherent, in the

single anticipating reference. *Continental Can Co. v. Monsanto Co.,* 948 F.2d 1264, 1268 (Fed. Cir. 1991). Other precedents of the court have held that inherent anticipation does not require that a person of ordinary skill in the art at the time would have recognized the inherent disclosure. E.g., *In re Cruciferous Sprout Litig.,* 301 F.3d 1343, 1351 (Fed. Cir. 2002); *Mehl/Biophile Int'l Corp. v. Milgraum,* 192 F.3d 1362, 1366 (Fed. Cir. 1999) ("Where the result is a *necessary consequence* of what was deliberately intended, it is of no import that the article's authors did not appreciate the results."); *Atlas Powder*, 190 F.3d at 1348-49 ("Because 'sufficient aeration' was inherent in the prior art, it is irrelevant that the prior art did not recognize the key aspect of [the] invention. An inherent structure, composition, or function is not necessarily known."). In the instant case, the unappreciated anticipation of the properties of beta-blockers, such as timolol to inhibit sodium-hydrogen antiport activity while it is reducing intraocular pressure also does not require recognition. Applicant claims to have discovered the method of modulating aqueous secretion by modulating the antiports of the aqueous humor. Since the pharmaceutical compositions claimed by Applicant produced the claimed modulation of aqueous secretion, the discovery of the modulation at the antiport is inherent. In the context of the accidental anticipation, beta-blockers, such as timolol, do not accidentally modulate the antiport when the pharmaceutical composition is applied to a patient in need of treatment. The antiport necessarily and inevitably is modulated when the beta-blocker is applied and does not require a skilled artisan to recognize the inherent characteristic in the prior art that anticipates the claimed invention. Regarding administration Applicants asserts that the reference

differs because it is not administered to the ciliary epithelial cells, however, the Examiner consulted the instant specification for information on how one would administer the NHE inhibitor (beta blocker) to the ciliary epithelial cell without administering an eye drop to the eye. The specification teaches that modulation compounds of the present invention can be administered ophthamologically and also topically and preferably, administered to the eye topically (see page 18, lines 29-32). Drug Facts and Comparisons teach administration of beta blockers, such as timolol, to the eye ophthalmically for reduction of intraocular pressure and treatment of glaucoma. Applicant relies on Verdegaal Brothers, Inc. v. Union Oil Co. of Calif., 2 USPQ2d 1051, 1053 (Fed. Cir. 1987)" and states that ("Inherency may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.)." In response, probabilities or possibilities are not required in the case of inherency. In the instant case, the unappreciated anticipation of the properties of beta-blockers, such as timolol to inhibit sodium-hydrogen antiport activity while it is reducing intraocular pressure also does not require recognition. Applicant claims to have discovered the method of modulating aqueous secretion by modulating the antiports of the aqueous humor. Since the pharmaceutical compositions claimed by Applicant produced the claimed modulation of aqueous secretion, the discovery of the modulation at the antiport is inherent. Applicant argues that Drug Facts and Comparisons teach prophylactic utility and the instant claims are drawn to "therapeutic use". In response, Drug Facts and Comparisons is drawn to

treatment of elevated intraocular pressure or glaucoma which would encompass therapeutic treatment.

Claims 94-96, 99-104, 107-110, 112, and 113 are rejected under 35 U.S.C. 103(a) as being unpatentable over Adorante et al. U.S. Patent No. 5,559,151 and Cherksey U.S. Patent No. 4,950,591.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Applicant argues “Examiner's conclusion, based on the premise that it would have been obvious to "employ two agents well known to treat glaucoma/ocular hypertension together to treat the very same condition" is incorrect because “Applicants neither teach, nor claim, treatment of glaucoma, nor ocular hypertension”. In response, Independent claim 94 is drawn to “a method for therapeutically reducing aqueous humor inflow” and as a result 'reducing net inflow in aqueous humor formation". Dependent claim 103 is drawn to treatment wherein a human or animal subject has **glaucoma** and dependent claim 104 is drawn to treatment wherein the human or animal subject has elevated intraocular pressure. Independent claim 108 is drawn to “regulating salt uptake or release in aqueous humor formation and reducing net inflow". Currently treatment for glaucoma and elevated intraocular pressure is directed to reducing formation of aqueous humor and reducing inflow of aqueous humor and increasing

outflow of aqueous humor. The same eyedrop(s) is(are) applied to the eye to produce the same results, modulation/reduction of intraocular pressure by reducing inflow. Applicant argues that "the combined reference teaches only the use of chloride- channel blockers (Adorante uses DIDS; Cherksey uses an amiloride based gel) in NPE cells, without any reference what-so-ever to bicarbonate-chloride exchange. The chloride channel is not even shown in Applicants' Figures". In response, Applicant defines the anion exchanger isoform 2 (AE2) as 4,4'-diisothiocyanatostilbene-2,2'-disulfonate (DIDS) (see instant claims 99 and 100). Adorante et al. teach that DIDS treats glaucoma and/or ocular hypertension by inhibiting aqueous humor formation and thus, lowering IOP. Cherksey teaches amiloride and its derivatives for reduction of intraocular pressure. The nature of the problem to be solved, regulating intraocular pressure or regulating salt uptake or release by ciliary epithelial cells to modulate the aqueous humor would have led one of ordinary skill in the art to choose an appropriate agent to lower intraocular pressure and regulate salt uptake/release. Cherksey teaches that amiloride, (by Applicant's own definition is an NHE inhibitor) lowers intraocular pressure and Adorante et al. teach that DIDS (by Applicant's own definition is an AE2) lowers intraocular pressure and blocks chloride channels in the ciliary epithelium. Therefore, it would have been obvious to use both DIDS and amiloride in combination to lower intraocular pressure and regulate salt uptake or release by the ciliary epithelium. Further, as stated supra, and in *In re Best* and *In re Fitzgerald* (205 USPQ 594 (CCPA 1980)), the mere recitation of newly-discovered function or property, inherently possessed by things in prior art, does not cause claims drawn to those things to

distinguish over prior art. In such a situation, the burden is shifted to the applicant to prove that subject matter shown to be in prior art does not possess characteristic relied on where it has reason to believe that functional limitation asserted to be critical for establishing novelty in claimed subject matter may be inherent characteristic of prior art; whether rejection is based on "inherency" under 35 U.S.C. 102, on "prima facie obviousness" under 35 U.S.C. 103, jointly or alternatively, burden of proof is same.

Claims 94-98, 102-104, 107-110, 112, 113 and 115 rejected under 35 U.S.C. 103(a) as being unpatentable over Brandt et al. U.S. Patent No. 5,585,401 and Cherksey U.S. Patent No. 4,950,591.

Applicant argues that “Applicants’ neither teach, nor claim, treatment of glaucoma, nor ocular hypertension.” In response, Independent claim 94 is drawn to “a method for therapeutically *reducing aqueous humor inflow*” and as a result *'reducing net inflow in aqueous humor formation*". Dependent claim 103 is drawn to treatment wherein a human or animal subject has *glaucoma* and dependent claim 104 is drawn to treatment wherein the human or animal subject has *elevated intraocular pressure*. Independent claim 108 is drawn to “regulating salt uptake or release in aqueous humor formation and *reducing net inflow*". Currently treatment for glaucoma and elevated intraocular pressure is directed to reducing formation of aqueous humor and reducing inflow of aqueous humor and increasing outflow of aqueous humor. The same eye drops are applied to the eye to produce the same results, modulation/reduction of intraocular pressure by reducing inflow. Applicant asserts that there are many different

components recognized in the prior art to control intraocular pressure and the identification of a method in the prior art that affects one part of this complex in no way necessarily precludes the invention of another method of “selectively controlling" a completely different region of the eye. In response, as noted in *In re Best* (195 USPQ 430 (CCPA 1977)), and *In re Fitzgerald* (205 USPQ 594 (CCPA 1980)), the mere recitation of newly-discovered function or property, **inherently possessed** by things in prior art, does not cause claims drawn to those things to distinguish over prior art. In such a situation, the burden is shifted to the applicant to prove that subject matter shown to be in prior art does not possess characteristic relied on where it has reason to believe that functional limitation asserted to be critical for establishing novelty in claimed subject matter may be inherent characteristic of prior art; whether rejection is based on "inherency" under 35 U.S.C. 102, on "prima facie obviousness" under 35 U.S.C. 103, jointly or alternatively, burden of proof is same. Applicant states that Brandt’s reference is irrelevant because bumetanide is ineffective in lowering IOP in vivo, citing Tian et al. as evidence. In response, Brandt et al. teach lowering of intraocular pressure with bumetanide. Every patent is presumed to be valid. 35 U.S.C. 282, first sentence. Public policy demands that every employee of the United States Patent and Trademark Office (USPTO) refuse to express to any person any opinion as to the validity or invalidity of, or the patentability or unpatentability of any claim in any U.S. patent, except to the extent necessary to carry out

(A) an examination of a reissue application of the patent,

(B) a reexamination proceeding to reexamine the patent, or

(C) an interference involving the patent.

The question of validity or invalidity is otherwise exclusively a matter to be determined by a court. Likewise, the question of enforceability or unenforceability is exclusively a matter to be determined by a court. See MPEP 1701 [R-3]. Further in response to administration to live monkeys and mice, the claims are drawn to treatment of a human or animal, hence the instant claims are not limited to monkeys and mice. Applicant states that Cherksey's method of reducing intraocular pressure by administering amiloride is not Applicant's invention. Cherksey teaches amiloride and its derivatives for reduction of intraocular pressure. The nature of the problem to be solved, regulating intraocular pressure or regulating salt uptake or release by ciliary epithelial cells to modulate the aqueous humor would have led one of ordinary skill in the art to choose an appropriate agent to lower intraocular pressure and regulate salt uptake/release. Cherksey teaches that amiloride, (by Applicant's own definition is an NHE inhibitor) lowers intraocular pressure and Brandt et al. teach that bumetanide (by Applicant's own definition is an inhibitor of a Na+-K+-2Cl- symport) lowers intraocular pressure and blocks chloride channels in the ciliary epithelium. Therefore, it would have been obvious to combine bumetanide and amiloride in combination to lower intraocular pressure and regulate salt uptake or release by the ciliary epithelium. The idea of combining them flows logically from their having been individually taught in the prior art

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Donna Jagoe whose telephone number is (571) 272-0576. The examiner can normally be reached on Monday through Friday from 8:00 A.M. - 4:30 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne (Bonnie) Eyler can be reached on (571) 272-0871. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/YVONNE L. EYLER/
Supervisory Patent Examiner, Art Unit 1619

Donna Jagoe /D. J./
Examiner
Art Unit 1619

March 23, 2010